IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: H. William Bosch et al.

Title: NOVEL NIMESULIDE COMPOSITIONS

Appl. No.: 10/697,703

Filing Date: 10/31/2003

Examiner: Tristan J. MAHYERA

Art Unit: 1615

Confirmation 8369

Number:

DECLARATION UNDER 37 CFR 1.131

Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450

Sir:

I, H. William Bosch, hereby declare and state that:

- I am a citizen of the United States, residing at 237 Rodney Circle, Bryn Mawr, PA 19010.
- At the time of events detailed in paragraph 4, infra, I was an employee of Elan Drug Delivery, Inc., with offices at 3500 Horizon Drive, King of Prussia, PA 19406.
- I am a co-inventor of the invention disclosed and claimed in the above-referenced application.

Atty. Dkt. No. 029318-0973 Appl. No. 10/697,703

- 4. Prior to June 27, 2003, I instructed my associates, as part of my supervisory role, to prepare nimesulide compositions comprising particles of nimesulide or a salt thereof having an effective average particle size of less than 2000 nm and at least one surface stabilizer adsorbed on the surface of the particles. My work relating to preparing the nimesulide compositions, which occurred prior to June 27, 2003, is documented in the attached exhibits.
- As shown in Exhibit A (Notebook No. 5822, pages 006-008), the formulation comprising 5% nimesulide and 1% Plasdone® S-630 provides a stable nanoparticulate nimesulide composition.
- As shown in Exhibit B (Notebook No. 5822, pages 009-011), the formulation comprising 5% nimesulide and 1% Plasdone[®] S-630 provides a stable nanoparticulate nimesulide composition.
- As shown in Exhibit C (Notebook No. 5822, pages 012-014), the formulation comprising 5% nimesulide, 1% Plasdone[®] S-630 and 0.2% DOSS provides a stable nanoparticulate nimesulide composition.
- As shown in Exhibit D (Notebook No. 5822, pages 015-017), the formulation
 comprising 5% nimesulide, 1% Plasdone® S-630 and 0.05% sodium lauryl sulfate (SLS)
 provides a stable nanoparticulate nimesulide composition.

Atty. Dkt. No. 029318-0973 Appl. No. 10/697,703

D. William Bosch

9. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent resulting therefrom.

H. William Bosch



élan			OK NO. 5822	Page 00	6 of 20
Title Nimesulide	(5%	API 11%	5-630)		
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(cont. from pg05	,				
(cont. nom pg	,				
				100 mg 2000000 mg 20000000	
Batch Record	for Dispersion	Technology M	lilling Procedu		The second second
			iming Frocedu	res	-
I. General Inf	formation				
Name	Christian L	Nert-			า
Date		·-			
Formula	5%- Nimes	relieder 10%	5-630		
Continued on Page	007				
II. Quantities I	Dispensed				***
	- ispensed				
	Quantity	Туре	Source	Lot Number	1
Media	80 6	Polymill 200	DOW / PMRS	Lot Number	
Drug Substance	4.25	Ninein lide	Sigma		1
Stabilizer	0.85	5-630	39***		
Water Other	79.9	PI			
Other					
III. Process Para	meters				,
Milling Method	Dung will 1	150 4 batch c	hamber) F91	- a e	
Mill Speed	7,200 70	n	EUTHERY 1 11	2 (E MM .205	
Temperature	~10.0				
IV. Notes					
Milling Time: 9:5	3 - Start	milline : la:	31 - 1 1 0	`a (
10:5	3 - Second	sample : 11:	31 - first S 41 - third	Canable	
1:/	0 - Harrest		- I DIFA	Sumple.	
Quantity retained post r	nilling. C.	7 6			
Quantity retained post-r	ming. Torget	to tilter out	media before	Weighing	
* Did not filter our	t media ini	tally and	hecomolic ~	V- 5-11 .	
Did not filter out Later filtration	left ~20	me of	1 L	· L suspension	•
		medi	in Thee Juspe	ension.	
ONFIDENTIAL		201 -	(c	ont. on pg. 007)
	Signature	Chity 7. W	let	Date	
Reviewed ar		Kuls De		Date	-
				Date	

LABORATORY NOTEBOOK NO. 5822 Page 007 of 200

Title Nimefulide	(5 1/2 APT; 1 1/2 5-630)
(cont. from pg00	
Batch Record for	Dispersion Technology Milling Procedures
Name Date	Christian Wertz
Formula Continued from page	5 % ' Nimesulide 1% 5-630

IV. Particle Size Data

Particle Size Analyzer Used	HORIBA LA-910 (S# 8514870103D)
Standards Measured	Lot # 22579; mean = 200; Duke Sci; 200 nm Std

Elapsed Time	Mean, nm	D50, nm	D90, nm	Comments
46	173	156	285	No Sonication
ļ,	169	148	280	60 Sec. Sinication
60	150	124	256	No sonuation
	144	121	243	60 sec Sonication
108	3:161	140	14961	No Sonication
100	131	111	218	60 Sec. Sonication
197	10794	318	33156	No Sonication
7 .	140	112	246	60 Sec. Sonication
3 day	195	142	337	No Senication
	143	115	249	60 Sec. Sinication

* Cansed Which * Can in	begin to aggrega by reduction in could not be crease S-630 Co. 5121 data in to	particle size Compens ncentration	e (Increase in ated for with or add add	Surface area) h 11% S-630
CONFIDEN [®]	FLAI	re Chita	7. West	(cont. on pg00 8'



Title Nimecalide

Name

Formulation

Notebook reference Continued on page

Date

II.

(cont. from pg. _____077__)

General Information

Particle Size Data

LABORATORY NOTEBOOK NO. 5822 Page 008 of 200

5-630

10/0

(5% APT , 1% 5-630)

Particle Size Stability for Dispersion Technology Formulations

Christian F. Wests

\$ 50% Nimesialide

ticle Size Analy ndards Measure		Lot # 22	A-910 (SA 569 ; mean	= 200 nm !	Duke Sci 200mm Std.
lapsed Time	Storage Conditions	Mean, nm	D50, nm	D90, nm	Comments
3 days	5'6	195	142	331	No Sonuation
	5.0	143	115	249	60 Sec. Sunicition
5 days	5.0	176	112	322	no Sonication
	5°C	138	113	235	60 S Sunication
7 days	5°C	174	116	342	no Sonication
	5°C	139	110	248	60 S Sonication
4 days	5,0				
	2. 1				
Pata in	tolder 1	2 - 5.11	L. Letterson	16- 000	
	10100	- July 10	muriky 7	INC UPW	-5122-A
	_				(cont. on pg
IDENTIA	L		1011	1 1 1-	(some on pg
	L viewed and und	Signature	Kin V.	Nit	Date
D	damed and	1	1 6/11	- 6	/
	neweu and und	erstood by 🗥	-IWMINA	mulan	Date



LABORATORY NOTEBOOK NO. 5822 Page 009 of 200

Tille Nimesulide (5% ACT, 2% 5-630)
(cont. from pg)
-mix J-630 Slovly into DI Hzo W/ mild striving until algoried
-mix J-630 Slowly into DI H20 W/ mild stirring until alsowed -odd polymill 200 W/ gentle manual Stirring -add ArI W/ gentle stirring until thoroughly mixed
and me of yourse strong with thoroughly mean
Batch Record for Dispersion Technology Milling Procedures
I. General Information

Name	Christ	an Werts			
Date	L				
Formula	5 %	Nimetalide	, 2%	5-630	
Continued on Page	010				

Quantities Dispensed II.

	Quantity	Туре	Source	Lot Number
Media	80.6	Polymill 200	DOW	MM 00/D12
Drug Substance	4.25	Nimesulide	Sigma	117/1/1019
Stabilizer	1.70	5-630	ISP Tech.	ML900012974
Water	79.05	PΓ		
Other				

ш. Process Parameters

Milling Method	Dynomill (150 cc batch chamber)	F915@	Rm 205
Mill Speed	4200 rem		
Temperature	~10 'C		

IV. Notes

filling Time:	8:15	Sturt bate	ch : 9:15	1st Sambl	′.
	10 15	2nd Jamps	4. 11:15	Harvest	

			(cont. on pg	0/0)
CONFIDENT	Signature		Date_	1
	Reviewed and understood by	N. William Bosch	Date	

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Title _	Nimisulide	(5%	API	, 20%	S-630)	

(cont. from pg. _____0 9 ____)

Batch Record for Dispersion Technology Milling Procedures

Name	Christian West
Date	7
Formula	5 % APE 2 % J-630
Continued from page	009

IV. Particle Size Data

Particle Size Analyzer Used	HORIBA 14-910 (5# 8514870103D)
Standards Measured	Lot # 22529 , mean = 200 nm ; Pukesci 200 nm Sta

Elapsed Time	Mean, nm	D50, nm	D90, nm	Comments
60	156	136	255	No Sonication
	156	134	258	60 S sonication
120	125	109	201	no sonication
ļ	122	107	193	60 5 Sonication
180	144		260	no Sonication
	132	111	221	60 S Sonication
l				

· Pata in folder #2 supplementary folder OFW-5722 A

CONFIDENTIAL		. 1 1		(cont. on pg	011)
		Chut 7.			
Reviewed and un	nderstood by	N.Willra	m Bo	Date	-

le Nimeinlide	(5%	6 API	2 % S-1	(30)		
	(
0.00						
ont. from pg010	/					
Particle Size	Stability fo	r Dispersion	n Technolo	gy Formu	lations	
I. General I	nformation					ה
Name	Chris	tion Newt	<u> </u>			
Date		API , 26	r=/70			1
Formulation		API, AD	3-650]
Notebook reference Continued on page						<u>l</u> j
Continued on page						
II. Particle S				. D. T	27/11/201	71
Particle Size Analy	zer Used	HORIBA L	A-916 (S# 85148	5c: 1 200 nm Std.	1
Standards Measure	d	Lot # 2256	9; mean = 6	VO PIT I VAL	30. 1 2.2	
	C	Mean, nm	D50, nm	D90, nm	Comments	
Elapsed Time	Storage Conditions	Ivicuit, iun				
/ day	5°C	141	111	253	no sonication	
1	5.6	130	110	215	ne Senication	_ 1
3 lay	5.0	138	111	215	60 S Sonication	-
7 day	506	1-15	113	258	no sonication	
7 4189	5°C	134	112	226	no sonication	- '' -
21 144	5.0	154	/23	272	60 S SONICATION	
11 /	5°C	141	116	266	ne somicution	_
35 dag	50	145	12-1	246	60 5 Sonication	
				 		
 		+	-			
-						
	<u> </u>		 	 		
					ev CFW-5722 (cont. on pg	
CONFIDENT	AL	Signature	14. 4.5	7. Wit	Date Date	



Title Vime Statiste.

LABORATORY NOTEBOOK NO. 5822 Page 012 of 200

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Title Nime Stalide	5% API	1º1/0 S-630	0.2%	0055
(cont. from pg)				
Batch Record :		n Technology M	illing Proced	<u>lures</u>
Name	Christian F. W	ertz		
Date				
Formula		630, 0.2% DOSS		
Continued on Page	013			
II. Quantities D	ispensed Quantity	Time		
Media		Туре	Source	Lot Number
Drug Substance	80.6	polymill 200	DOW	MM001012
Stabilizer	4.25	Nimesulia	Sigma	11741019
Water	0.85	1-630	ISP Tech.	ML 9000 12974
Other	79.73	PI	Oute	Spaniller

III. Process Parameters

Milling Method	Dynomill (150 cc batch chamber) F915 @ room 205
Mill Speed	4200 rpm
Temperature	10 C

IV. Notes

Milling Time: 8:20	Start batch	1 9.20	14 .	Sample	
11:20	Harvest				
Quantity retained post-m					

	Ostarium	was sig	nill (an	tly U.	ss VII	cong	u/	Doss ;	than pre	VIOUS	runs
-	Dissolved	5-630	, the	n a	liffolice	1 Poss	· ~/	gentle	stirring	(-15	min
_	Westit	lack	L.	· : //		d			_ , , ,		

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Sign		Chite F. Wit	Date_ ,		
Reviewed and understo	od by	A William Bosch	Date	•	

Title Nimesulide 5 % Aft, 1 % 5-630, 0.2 % DOSS

Name	Chri	stian F. Wertz			
Date					
Formula	5%	API, 1% S-630, 0	.2% DOSS		
Continued from pag	e 012	012_			
IV. Particle S	ize Data				 1
Particle Size Analy	zer Used	HORIBA L	4-910 (s#: 851	14870103D)	-
Standards Measure		Lot #: 22569	9; mean = 204	5 ; Duke Sci.; 200 nm standard	
Elapsed Time	Mean, nm	D50, nm	D90, nm	Comments	
60	172	154	278	no Somicition	
	172	156	280	m concertion	
120	131	111	217	60 S Sinication	
	120	1 -//			
			 		
			 		
		_			
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Title Nimesulide	5-10	API,	1 %	5-630	0.2 %	₽055	

(cont. from pg. ___013___)

Particle Size Stability for Dispersion Technology Formulations

I. General Infor	mation
Name	Christian F. Wertz
Date	
Formulation	5% API, 1% S-630, 0.2% DOSS
Notebook reference	

II. Particle Size Data	
Particle Size Analyzer Used	HORIBA LA-910 (s#: 8514870103D)
Standards Measured	Lot #: 22569; mean = 203; Duke Sci.; 200 nm standard

Elapsed Time	Storage Conditions	Mean, nm	D50, nm	D90, nm	Comments	
1 day	5°C	136	116	22.3	he Senication	
' '	500	137	116	224	60 5 Sonication	
2 day	5°C	143	121	238	no sonication	_
	500	144	122	241.	60 s Sonication	
6 day	5°C	149	/33	239	no Sonication	_
	5.0	151	135	242	60 & Sonication	_
7 day	5°C	160	143	259	no Source tron	
,	5℃	163	146	261	60 S Sonication	_
21 day	5°C	162	150	252	ne senicetion	_
	5°C	166	155	255	60 & Someation	_
35 day	5°C	180	172	276	no sonicotion	_
,	5°C	187	180	280	60 5 Somuetion	_
					L	

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Reviewed and understood by A. William booch

5 % API . 1% 5-630 , 0.05 % SLS

- Plssowid J-630 in the fillowed by SLS under gentle mixing.
- SLS dissolved very rapidly of very little form

Туре Polymill 200

Nimesulide

S-630

H2O

SLS

Batch Record for Dispersion Technology Milling Procedures

5% API, 1% S-630, 0.05% SLS

Christian F. Wertz

Quantity

80.6 4.25

0.85

79.86

0.04



Title Vinesulide

Name Date

Formula Continued on Page

Media

Water

Other ***

Stabilizer

Drug Substance

(cont. from pg. _____)

General Information

Quantities Dispensed

Process Parameters

tood board board to

LABORATORY NOTEBOOK NO. 5822 Page 015 of 200

Source

DOW

Sigma

ISP Technology

DI

Lot Number

MM001012

117H1019

ML900012974

Milling Method	Dynomill (150 cc batch chamber) F915 @ room 205
Mill Speed	4200 rpm
Temperature	10 C
IV. Notes	
Milling Time: 1:	22 Start batch; 9:22 1st sample
<i>[0:</i>	22 Harrest
Quantity retained po	ost-milling: 67.4 9 (80.7 h+ %)
mili began leakin	rig after first sumple mas taken from mill
	(cont. on pg
NFIDENTIAL	Signature Cluth 7. Westy Date
	n///i/
Review	ed and understood by Mhullanin Bosch Date

Title Nimesulide 5% API, 1% 5-630 0.05% SLS

Batch Record for Dispersion Technology Milling Procedures

5% API, 1% S-630, 0.05% SLS

D50, nm

154

157

104

105

HORIBA LA-910 (s#: 8514870103D)

D90, nm

288

211

178

175

Lot #: 22569; mean = 200 ; Duke Sci.; 200 nm standard

no Sinication

60 S Sonication

60 S Sonication

no sunication

Comments

Christian F. Wertz



(cont. from pg. 015)

Name

Date Formula

IV.

Continued from page

Standards Measured

Elapsed Time

60

120

Particle Size Data Particle Size Analyzer Used

Mean, nm

174

176

116

117

' Pala	in lotter	*= Supplem	entary fokler	0FW-5822_/	4
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Title Nurresulide	5% All, 11/6 5-630, 0.05% SLS	

(cont. from pg. __0/6___)

Particle Size Stability for Dispersion Technology Formulations

 General Infor 	mation
Name	Christian F. Wertz
Date	
Formulation	5% API, 1% S-630, 0.05% SLS
Notebook reference	
Continued on page	

II. Particle Size Data

Particle Size Analyzer Used	HORIBA LA-910 (s#: 8514870103D)		
Standards Measured	Lot #: 22569; mean =	; Duke Sci.; 200 nm standard	

Elapsed Time	Storage Conditions	Mean, nm	D50, nm	D90, nm	Comments
3 day	5-6	j 23	108	192	no Sonication
/	506	123	108	193	60 S Sonication
5 day	5°C	127	110	203	no Sonkation
,	5°C	127	110	205	60 S Sonceation
7 duy	5°C		113	217	no sonuation
,	5.6	134	113	219	60 S Somication
21 day	5°L	126	110	199	no someotion
/	5°C	127	109	205	60 S Someation
35 day	5°C.	141	120	234	no Sovication
	500	142	119	237	60 S Somication

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